A basal stem cell signature identifies aggressive prostate cancer phenotypes.

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Public Summary:
Aggressive cancers often possess functional and molecular traits characteristic of stem cells. Specifically in prostate cancer, tumors of advanced metastatic disease overexpress certain stem cell associated genes and signaling pathways compared to localized disease. It is unclear if aggressive forms of prostate cancer resemble normal stem cells residing within the human prostate at the molecular level. Using a combination of cell sorting, next-generation sequencing, and computational methods, we profiled highly purified cell populations from the human prostate and showed that aggressive prostate cancer is enriched for a prostate basal stem cell signature. Sequencing data showed that the two cell populations (basal and luminal) were molecularly different with the basal population defined by genes associated with stem cell signaling programs and invasiveness. We developed a 91-gene basal stem cell signature and applied this signature to datasets from prostate cancer patients that varied in their disease progression. Late-stage metastatic prostate cancer was molecularly more stem cell-like than early-stage, localized prostate cancer. Interestingly within heavily treated prostate cancer metastases, subtypes had varying enrichment of the stem cell signature, with the highly aggressive small cell neuroendocrine carcinoma being the most stem cell-like. We further found that this aggressive subtype and the normal prostate basal stem cell share a core set of genetic qualities. Taken together, our results suggest that targeting normal stem cell traits could potentially be a new strategy for treating advanced prostate cancer.

Scientific Abstract:
Evidence from numerous cancers suggests that increased aggressiveness is accompanied by up-regulation of signaling pathways and acquisition of properties common to stem cells. It is unclear if different subtypes of late-stage cancer vary in stemness properties and whether or not these subtypes are transcriptionally similar to normal tissue stem cells. We report a gene signature specific for human prostate basal cells that is differentially enriched in various phenotypes of late-stage metastatic prostate cancer. We FACS-purified and transcriptionally profiled basal and luminal epithelial populations from the benign and cancerous regions of primary human prostates. High-throughput RNA sequencing showed the basal population to be defined by genes associated with stem cell signaling programs and invasiveness. Application of a 91-gene basal signature to gene expression datasets from patients with organ-confined or hormone-refractory metastatic prostate cancer revealed that metastatic small cell neuroendocrine carcinoma was molecularly more stem-like than either metastatic adenocarcinoma or organ-confined adenocarcinoma. Bioinformatic analysis of the basal cell and two human small cell gene signatures identified a set of E2F target genes common between prostate small cell neuroendocrine carcinoma and primary prostate basal cells. Taken together, our data suggest that aggressive prostate cancer shares a conserved transcriptional program with normal adult prostate basal stem cells.